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THE ACTION OF EPINEPHRIN IN MINIMAL DOSES UPON BLOOD PRESSURE AND THE MECHANISM OF THIS EFFECT

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THE ACTION OF EPINEPHRIN IN MINIMAL DOSES UPON BLOOD PRESSURE AND THE MECHANISM OF THIS EFFECT.

By

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The problem undertaken by us in this work was to determine the effect of epinephrin in minimal doses upon the blood pressure, and to discover, if possible the mechanism of this action.

It has long been assumed that the substance epinephrin, or as it is known commercially, adrenalin, was purely presser in its effect upon the blood pressure. OLIVER & SCHAEFER,(1) who first reported upon the blood-pressure raising power of adrenalin when intravenously injected, did not observe a depressor effect. CYBULSKI & SCYMONOWICZ (2) who noted the presser effect about the same time as the English workers, likewise overlooked the fall of blood pressure. ELLIOT (3) working ten years later, enunciated the theory of the myoneural junction as the point of action of adrenalin, but declared, concerning the depressor effect, that "straightforward experiment fails to prove vascular dilatation". The most recent books on the subject of the ductless glands omit a consideration of the fall of blood pressure incident to the injection of adrenalin. BIEDL (4) in "Die Innere Sekretion" overlooks this effect, summarizing thus: "The characteristic action of adrenalin is the raising of arterial blood-pressure". He mentions, however, that in cats and rabbits a maintained fall of blood-pressure is sometimes noted. VINCENT (5) in his recent "Inner Secretions and Ductless

Glands" disregards the fall, intimating that it is seen only as the depressor effect of the tissue extract in which the epinephrin is contained. The modern physiologies, HOWELL (6), TIGERSTEDT (7) and others still omit all mention of a depressor effect.

That a depressor effect actually exists, however, may be seen from infrequent references in the literature to it. As early as 1899 it was niticed and reported upon simultaneously by LEWANDOWSKY (8) and by BARDIER & FRAENKEL (9) MOORE & PURINGTON (55) also described the depressor effect. More recently HOSKINS & McCLURE (10) have published an article in which it is affirmed that the characteristic primary effect of adrenalin is the lowering of blood pressure. It is on this basis that they attack the theory that the function of the adrenal glands is to maintain vascular tone. They point out first, that the quantity of epinephrin normally in the circulating blood is far below the dose necessary to cause the pressor effect; second, that a dose of this dilution usually causes a fall of blood pressure rather than a rise; third, that doses of adrenalin so small as to have no effect upon the systemic blood pressure, cause an inhibition of the peristaltic movements of the intestines; (11) and (12) and fourth, that ligation of the adrenal vessels does not result in an immediate fall of blood pressure. (13) Other workers have shown (See Tigerstedt's Text Book of Physiology) that it is impossible to prolong the life of an experimental animal deprived of its adrenal glands beyond 24 hours by the in-

jection of adrenelin.

CANNON and various of his associates (De la Paz, Shohl, Wright, Washburn, Lyman, Nice, Gruber, Osgood, Gray, Mendenhall) (14, 15, 16) have advanced the theory of "special stress," i.e. that the adrenal glands are part of the mechanism for the development of excess power in times of special need. This theory lays particular emphasis upon the similarity between the glycosuria seen after repeated injections of adrenalin and the glycosuria following emotional excitement. But it likewise takes cognizance of the facts pointed out by Hoskins & McClure and accepts the fact that adrenalin is possibly depressor in minimal doses.

Various theories have been proposed for the explanation of the depressor effect of adrenalin. DALE (17) showed that the depressor effect of adrenalin was alone retained after paralysis of the vaseconstrictors by ergot, although Ball $_2$ and pituitarin which act directly upon the muscle, still give the pressor effect. Hence he suggests that vasodilators are stimulated by adrenalin.

NEUJEAN (18) suggests that either the vaseconstrictors are only feebly stimulated in cases of a preponderant fall of blood pressure, or else they are first stimulated and then paralyzed, giving relaxation and consequent hypotension.

The MELTZERS (19) conclude, after careful experimentation upon the ears of rabbits, that adrenalin stimulates both constrictors and dilators centrally, and also stimulates

the constrictors peripherally. They believe that larger doses favor constriction and smaller doses favor dilation (which bears out the recognized teaching that the constrictors are the more powerful and the dilators the more sensitive.) Hence they explain the rise-and-fall following a medium sized dose thus: the primary effect of the large dose is constriction, resulting in hypertension, but as the adrenalin is oxydized in the tissues the dose becomes progressively reduced until it becomes of the strength which causes the depressor effect, and hypotension results. In absence of central innervation, hypertension results by virtue of the peripheral mechanism, and hypotension does not follow.

This theory was combatted by NEUJEAN (18) who showed that hypotension did result from adrenalin injections after section of the cord. This was corroborated by CANNON and LYMAN (20)

Arguments against Dale's theory, against Neujean's theory, and against the theory proposed by the Meltzers are advanced by CANNON & LYMAN (20) They, in turn, suggest that vasoconstriction and vasodilitation may constitute two different responses of the same musculature to the same type of stimulus, the difference being due to a difference in the state of tonic contraction, or tonus in which the muscle is when the stimulus is received.

As we shall show later, we believe this theory is likewise fallacious and capable of being disproved.

In contrast to these elaborate theories of the cause of the depressor effect, a few writers still believe that the depressor effect is not due to any physiological action of adrenalin, but results from certain extraneous factors.

WEIDLEIN (21) compares commercial epinephrin and purified epinephrin, showing that the former usually produces a rise of blood pressure followed by a fall, whereas the latter never gives the succeeding fall. This he ascribes to (1) impurities in the adrenal glands which are not removed during the commercial process and (2) to decomposition products. BURKET (22) confirms this work in a brief report.

McQUIGAN & MOSTROM (23) ascribe the depressor effect to five causes, viz.,

(1) Cholin bases formed by decomposition

(2) Acids used as preservatives.

(3) Fatigue products resulting from repeated injections.

(4) Individual peculiarities of different animals.

(5) Nervous shock resulting from the cumulative effect of adrenalin injections.

VINCENT (5) in his text book intimates that the effect is due to the depressor effect of the tissue extract.

These non-physiological explanations are hardly necessary for further consideration. Weidlein's objections and the first two objections of McQuigan & Mostrom are well

controverted by CANNON & LYMAN (20) and the suggestion of Vincent is ruled out when crystalin adrenalin in distilled water is used. The last three objections made by McQuigan and Mostrom to a physiological interpretation of the fall, we have taken up in a later section of this paper,

APPARATUS AND METHODS.

The solutions used by us in our experimental work were all made up fresh for each experiment. In most cases Parke-Davis adrenalin (crystallin) was used; in two experiments epinephrin as prepared by Abel, and Parke-Davis Adrenalin-hydrochloride were used. Distilled water was used to make the dilutions in all cases. A solution of 1 to 100,000 was first prepared and this was used to make further dilutions. A hypedermic syringe graduated to hundredths of a cubic centimeter and furnished with a blue glass plunger was employed, thus enabling us to give very minute doses with great accuracy. We found it expedient, however, to lower the dose by dilution rather than by decreasing the size of the dose, since the percentage of error introduced is less.

The animals used were rabbits, cats, and dogs. The rabbits were usually anesthetized with ether; in a few cases urethane by stomach tube was administered but this was found to be less satisfactory. The cats were in all cases anesthetized directly with ether; The dogs were in most cases

given a previous injection of morphine. Several hours later they were anesthetized and the experiment performed.

The surgical procedure was usually very simple. A tracheal canula was employed in all cases to maintain a constant anesthesia. Blood pressure records were made by inserting a canula in the carotid or femoral artery and connecting it with a mercury manometer. The injections of adrenalin were made by means of the hypodermic needle into the jugular or femoral vein. A Jaquet clock was used to mark the time intervals.

In plethysmograph experiments, various types of plethysmograph were used. For the intestine a short glass cylinder suggested by Mr. Hedges was found to be quite sensitive and very convenient. In all cases only a loop of the intestine was plethysmographed, after being ligated off and severed from the main gut. Care was taken in all cases to include two or more larger vessels. For plethysmographing the leg, a larger cylinder was used, and attachment was made to the leg by means of a band of thin rubber, which was securely fastened onto the plethysmograph. The heart was plethysmographed after opening the chest under artificial respiration by means of the Erlanger intermittent blast, and a bell shaped plethysmograph was used. The kidney was plethysmographed with the same type of instrument.

The liver offered more difficulties, however. For this a plaster of paris plethysmograph was devised which just enclosed the extreme left lobe of the dog's liver. Excellent

records were obtained by its use.

In some experiments, complete extirpation of organs was made, after ligation of the afferent and efferent vessels.

Perfusion of the limbs, of the spleen, and of the kidneys was also tried. We kept the animals alive and under the anesthetic in all cases, in order to preserve all nervous connections. Perfusion was made by means of Locke's solution, kept at a temperature of 37.5 degrees, and under oxygen pressure. The outflow from the vein of the organ was registered in some experiments by the drop method, the effect being determined by counting the number of drops registered during a given interval of time previous and following the injection. In other experiments the Wiggers' float recorder was used. In this apparatus the outflow from the vein is collected by a funnel and runs into one upright tube containing a float and marking pen. Thus deviations in the rate of filling of the two communicating cylinders will be evidenced by a wave in the oblique line registered by the pen upon the moving record.

In a few experiments we tried the effect of modified bleed pressure conditions, as hereinafter described. In a few cases, likewise, we tried the effect of subcutaneous doses upon the blood pressure.

In all the experiments the records were made upon a smoked paper running upon a long roll Huerthle kymograph, usually at a low rate of speed. In experiments seeking to determine the cardiac effect, a fast speed was employed.

I. WHAT IS THE ACTION OF ADRENALIN?

While the primary object of our experiments was to determine the effect of minimal doses of adrenalin, we did not confine ourselves to this dosage alone, but considered the effect of the injection of various doses of adrenalin, seeking in each experiment to establish the minimal dose for that animal and to observe the effect of that dose.

We came finally to certain general conclusions with regard to the factors controling the effect produced by intravenous injection which may be summed up roughly as follows:

The effect upon blood pressure of the intravenous injection of adrenalin varies:-

1. In different species of animals
2. In different individual animals of the same species.
3. In different stages of the experiment with the same individual animal.
4. With different forms of adrenalin.
5. According to the size of the dose and the rapidity of injection.

However, since most of the factors mentioned produce quantitative differences rather than qualitative, we will discuss here in detail only those resulting in a qualitative difference. The species of the animal used and the size of adrenalin are the most important factors in the determination

of the effect of intravenous injection.

Taking up the matter of variation with species, we may consider first the results on rabbits.

TABLE I. Quantitative Data.

Experiment 15. Solution factor reduced to 1/600,000

DOSES	PURE RISES	RISE FOLLOWED BY A FALL	PURE FALLS
0.05cc. to 0.15cc.	13	4	1
0.20cc. to 0.60cc.	11	0	0
0.70cc. to 2.00cc.	1	0	3

Pure rises occurred in 72% of the first arbitrary division here made, 100% in the second division, and 25% in the third. On the other hand rise-and-fall curves appear only in the first division, and with one exception, pure falls only in the third.

TABLE II. Qualitative Data.

Experiment 14, Doses reduced to 1/4,000,000

0.1 cc. Rise-and-fall.

0.7 cc. Rise-and-fall in one case, doubtful in a second.

1.0 cc. Rise-and-fall. Repeated this three times.

1.5 cc. Pure rise.

3.5 cc Pure rise.

4.0 cc. Pure rise.

6.5 cc. Pure rise.

Hence our conclusions regarding the effect of adrenalin upon the blood pressure of the rabbit are as follows:

With minimal doses, a rise of blood pressure followed by a fall.

With slightly larger doses, a pure rise.

With larger dose, probably a pure fall.

With maximum dose, death of the animal.

A summary of the most definite of our experiments with the cat may be tabulated roughly as follows:

TABLE 3. Quantitative data, I.

Solution factor reduced to 1/1,000,000

Injections followed by a pure rise, 33. Average dose, 1.10cc.

Injections followed by a pure fall, 64. Average dose, 2.00cc.

Injections followed by a primary rise, followed by a fall, 80. Average dose, 4.75cc.

A typical experiment may be summarized as follows:

TABLE 4. Quantitative Data, II.

Solution factor reduced to 1/1,000,000, Experiment 22.

DOSE	PURE RISE	RISE FOLLOWED BY A FALL	PRIMARY FALL
0.1cc. to 1.0cc.	3	0	1
1.0cc. to 10.0cc.	1	3	4

In this experiment the minimal dosage, 0.4cc. gave a pure rise twice in succession. The next dosage in size was 1.00cc.

However, in one experiment the minimal dose gave a primary fall, and a fall was the primary effect in the majority of small doses. In still another experiment the minimal dose

gave a fall, and repeated gave a rise-and-fall. No pure rises were obtained.

In still another experiment, again, no pure falls were obtained. Both epinephrin and adrenalin hydrochloride were tried but both failed to produce a primary fall.

In all experiments with the cat, the results are very hard to predict. But series such as the following are quite indicative that the pure rise and the primary fall occur with smaller doses than the rise-and-fall.

TABLE 5. Qualitative Data.

Doses reduced to basis of 1/500,000. Experiment 19.

1.00cc.	Rise followed by a fall.
0.80cc.	Same
0.60cc.	Same
0.50cc.	Same
0.40cc.	Same
0.30cc.	Same
0.20cc.	Same in some cases, primary fall in some cases.
0.15cc.	Same in some cases, primary fall in some cases, pure rise in some cases.
0.10	Pure fall in most cases, pure rise in a few, rise-and-fall once.

Obviously, the minimal dose was not reached in this experiment.

On the basis of the data in the averages of all the injections as presented in TABLE 3, we think it is probable that the primary effect of adrenalin in minimal doses is a rise

of blood pressure. At a dose very slightly higher than this, however, it is certainly more usual to obtain a primary fall.

Thus to summarize, the effect of adrenalin injected intravenously into the CAT is as follows:

With minimal doses, probably a pure rise.

With slightly larger doses, a primary fall.

With large doses, a rise and fall, the fall showing the greater departure from the normal.

The dog is a much more pleasing animal with which to work because the results are so much more constant than in either the cat or the rabbit.

To state our conclusion first, we believe that the effect of minimal doses of adrenalin intravenously injected into the dog is a rise of blood pressure. For this we give the following experimental corroberation:

1. We were repeatedly able to get a series showing with the medium dosage a rise-and-fall; with a smaller dose a disappearance of the fall, and likewise with a larger dose a disappearance of the fall.

2. A compilation of data in the case of 14 dogs in which the effects of minimal doses were carefully sought for shows that in 12 of the 14 dogs, pure rises were obtained, and in only three were pure falls obtained.

3. Of the 14 dogs experimented upon for minimal effects 9 gave as the minimal dose effect a pure rise.

3 " " " " " " primary fall.

2 gave both rises and falls.

4. In no single experiment was the only result of the minimal dosage a primary fall. In each case where a primary fall was obtained, the same dosage at some other time in the experiment evinced a pure rise.

5. In experiment 13, where a primary fall occurred as one of the minimal effects, the following series was compiled:

TABLE 6. Qualitative Data. Experiment 13.

Doses reduced to basis of 1/1,200,000

.05cc. gave pure rise once and primary fall once.

.10cc. gave only rise-and-falls.

.15cc. gave primary fall.

.20cc. gave only rise-and-fall.

.30cc. gave rise-and-fall twice, primary fall once.

This indicates that while a primary fall may occur with the minimal dosage in a few rare cases, it may also occur after doses considerably above the minimal effect. The primary fall, however, stands out as the exception and the normal response seems to be a rise for minimal doses.

6. The following table gives quantitative data in confirmation of this proposition.

TABLE 7. Quantitative Data. Doses reduced to basis of 1/1,000,000 solution

Exp.	Minimal dose.	Effect.	Number of times.
1	1.00 cc.	Pure rise	Once.
	1.00 cc.	Primary fall	"
2.	0.50 cc.	Pure Rise	"
3.	6.00 cc.	"	"
4.	0.25	"	"

TABLE 7. (Continued)

Exp.	Minimal dose.	Effect.	Number of times.
7.	0.25 cc	Pure rise	Once
9.	0.30 cc to 1.00	"	Four
10.	0.15 cc to 0.80	"	"
11.	0.70 cc to 3.00	"	"
12.	0.20 cc to 5.00	"	Thirteen.
13.	0.04 cc	"	Once
	Same	Primary fall	"
17.	0.08	"	Twice
	Same	Rise	Once
29.	0.03	"	Four
30--31	0.25-0.50	Rise-and-fall	Five times

To summarize the conclusions relative to the effect in dogs, we believe that the effect of intravenous injection of adrenalin is the following:

With minimal doses, a pure rise.

With larger doses, a rise followed by a fall.

With maximum doses, a pure rise.

The primary falls which occasionally are seen we regard as exceptions, and so far inexplicable.

The summary of the blood pressure effects of adrenalin in the cat, rabbit, and dog is presented in chart form in TABLE 8.

TABLE 8.

BLOOD PRESSURE EFFECT OF INTRAVENOUS DOSES OF ADRENALIN

	RABBIT	CAT	DOG
EFFECT OF MINIMAL DOSES	Rise and fall	Probably pure rise	Pure rise
EFFECT OF SLIGHTLY LARGER DOSES	Pure rise	Primary fall	Rise and fall equal in size
EFFECT OF LARGE DOSE	Primary fall, usually	Rise-and-fall greater	Rise-and-fall Rise more marked.
EFFECT OF MAXIMUM DOSE	Death		Pure rise
OCCURRENCE OF PURE FALL	Frequently with large doses	Commonly with very small doses	Rarely, and then usually with small doses

II. WHAT IS THE MECHANISM OF THE RISE OF BLOOD PRESSURE?

Having determined the nature of the response of blood pressure to intravenous adrenalin injections, we turn next to a consideration of the question, "By what mechanism is this response produced?" To determine this it is necessary to consider separately the various portions of the response, and so we shall take up first the mechanism causing the rise.

The literature has long been in agreement on the point that the rise of blood pressure results primarily from vaso-constriction. Says BIEDL (4) in summarizing the present conception,

"The characteristic action of adrenalin, the raising of arterial blood-pressure, is due primarily to an increased peripheral resistance resulting from the constriction of capillaries and the narrowing of the lumina of the middle and smaller sized arteries through a heightening of the tonus of their circular musculature..... The constriction is due in part, also, to central stimulation of the vasoconstrictor center but this is possibly due to the stimulation caused by the anemia secondary to the primary effect of adrenalin. Most of the effect is produced peripherally, but not all of the peripheral vessels respond similarly".

The modern physiologists and pharmacologists generally adhere to this view. CUSHNY (24) summarizes by stating that while the rise in blood pressure is "for the most part

due" to constriction of "the vessels of the abdominal cavity, it is also aided by increased cardiac efficiency."

Other writers emphasize the central effect. The MELTZRS have been especially insistant upon the importance of this factor.

We have not attempted any experiments to test the theory of central stimulation. It suffices that several workers as described above have obtained the typical curves both before and after decerebration of transection of the cord.

As to the cardiac factor, however, so much contradiction occurs in the literature that we began an independent investigation. It might be noted that while some authors are convinced of an accelleration in rate others are persuaded that there is a retardation. MILLER, (25) and again DONALDSON (26) working clinically, and HOSKINS & LOVELLETTE working experimentally notice an increase in rate. OLIVER & SCHAEFER (1) likewise describe the effect as "augmentation and accelleration". On the other hand the standard texts on physiology and pharmacology give for the effect a "marked slowing of the heart" (HOWELL (13) CUSHNY (24) GASSER & MEEK and later MEEK & EYSTER (29) have shown by very careful experimentation using the electriocardiagraphic method of recording the rate that in the normal animal the rate is slowed by small injections of adrenalin.

It should be noted here that increased rate is an entirely different effect from that of increased efficiency, which refers to the total output. That the heart efficiency

is increased by adrenalin, although it be slowed in rate, is attested to by many authors, including Von Cyon (30) GOTTLIEB (31) CUSHNY (24) and others.

Our experiments upon the cardiac effect brought out these points: Rapid-rate kymograph records made an accurate counting of the rate possible. In practically all cases a decreased rate was observed. This decrease took place during the rise and in a few cases was continued over into the period of hypotension. In no case did it occur prior to the rise of blood pressure:

In a few exceptional cases a slight accelleration was observed, but it is to be discounted for two reason, viz.

(1) It occurred only in animals where the blood pressure was abnormally low, either due to shock or otherwise.

(2) It was insignificantly small as compared to the rise of blood pressure. For example, In one case the Acceleration amounted to 5% of the previous rate; the concomitant rise of blood pressure was 75% increase.

After vagotomy adrenalin of course accellerates the heart, heart muscle being very sensitive to the drug. The workers reporting accelleration with intact vagi, were doubtless working on animals with very low vagal tonus.

The second point brought out by our work was a confirmation of the work of GOTTLIEB and others mentioned above who held that the output of the heart was increased. This we found to be true by taking plethysmographic records, calibrating the piston recorder, and computing the actual increase in output.

That this increased efficiency is not responsible for the rise, however, is conclusively proved by this fact, that while in the great majority of cases an increased output was recorded, this increase took place not during or preceding the rise, but during the fall of blood pressure. Thus it could not be considered in any way causative of the rise of blood pressure.

The most probable cause of the initial rise following a small dose of adrenalin is of course vaso-constriction in some peripheral part of the circulatory tree.

It is noteworthy in this regard that BIEDL and other writers speak of "peripheral constriction" as if all the peripheral small vessels of the body were constricted. This is, however, as BIEDL later points out, very improbable, even with maximal doses. With smaller and with minimal doses, moreover, it is certainly not true, else it would be impossible to explain the cases of pure falls.

It is probable, however, that the rise of blood pressure is caused by peripheral constriction in certain organs, with a passive response on the part of other organs. We shall consider each organ separately giving the previous work done with our own experimental results following.

(1) The Skin.

This is so generally accepted as one structure which constricts upon the injection of even small doses of adrenalin, that we did not attempt any work upon it. The palor following the injections in man is a well marked clinical symptom. The

references to it in the literature are usually merely notes. (See LANGLEY (32), BIEDL (4), DONALDSON (26) MILLER (25). In no case is any effect but blanching noted.

(2) The Kidneys.

Concerning these vascular organs great contradiction occurs in the literature. That they constrict when perfused was shown by GOTTLIEB (33) in 1899. OLIVER & SCHAEFER (1) likewise report a diminution of size during injection of adrenalin. JONESCO, (34) showed that the kidney vessels constrict even before any effect is apparant in the general blood pressure. SOLLMAN (35) likewise PARI (36) pointed out, however, that while the kidney arterioles usually constrict, they sometimes dilate. BARDIER & FRANEKEL (9) (37) were convinced that dilatation took place, using an oncometer in their experiments.

Our experiments confirmed in part the work of Jonesco, but we do not believe that constriction is the sole effect, in this point agreeing with Sollman and with Pari.

Perfusion of the kidney of dogs, without removing the organ from the body, showed in all cases a constriction. Using the plethysmograph, which we consider a more delicate register of the effect, we not only found the usual effect to be a diminution in the size of the kidney but that it preceded, as Jonesco pointed out, the systemic effect. This was followed, as we shall discuss later, by a dilatation immediately preced-

ing the fall of blood pressure.

That the kidney is not solely responsible for the rise is indicated by the fact that the typical effects were reproduced after complete extirpation of both kidneys.

Concerning the kidney, our conclusions are that it is one factor in causing the rise of pressure.

(3) The Spleen.

Concerning the spleen, BARDIER & FRAENKEL (9, 37) again showed a dilatation using the oncometrical method. OTT & SCOTT (38) have recently shown that it is increased in size by adrenalin. But BRODIE & DIXON (39) claim for it a "powerful contraction" and OLIVER & SCHAEFER (1) state that it "contracts enormously"

Our own work gave the following results:

Perfusion of the spleen without removal from the body of the animal, gives very constantly in the case of the dog, first a slight dilatation, then a marked constriction. Estimated by the number of drops per unit of time, the average dilatation was about 10%, and the consequent constriction was about 60%. These figures constitute an average of our results in all cases where definite results were obtained.

The actual behavior of the spleen is very hard to determine either by plethysmographic or perfusion experiments, because of the marked rhythmic contractions which take place in that organ.

Extirpation of the spleen did not apparently alter the character of the curves obtained in response to adrenalin injection.

Our conclusions in regard to the spleen, therefore, are that while a slight dilatation occurs, it is quickly followed by a marked constriction, and hence the organ is probably a considerable factor in the causation of the rise of blood pressure.

(4) The Liver.

We were not able to find any literature upon the action of adrenalin upon the liver, or the role played by it in the effects of intravenous injection of adrenalin. It is tacitly assumed by some authors (e.g. CUSHNY, (24)) that the liver contracts along with other abdominal organs to cause the rise.

We performed but one experiment upon the liver. A special plaster-of-paris plethysmograph was designed by Dr. Meek and one lobe of the organ was plethysmographed during the injection of adrenalin. A simultaneous record of blood pressure brought out the fact that while in every case the liver did indeed show constriction, the constriction began only as the blood pressure was receding from the maximal point, and became most marked at the point of lowest pressure. From that point it regained its normal volume in a curve still parallel with the now returning blood pressure.

The significance of this constriction will be mentioned later. Suffice it to say here, in conclusion, that the liver for this reason is in all probability not concerned in the causation of the rise of blood pressure. It should be added that this refers of course, to relatively small doses. We do not attempt to state the effect upon the liver of large doses of adrenalin, but from this one experiment, it is certain that it is at least not a large factor, and probably not concerned at all, in the production of a rise with small doses.

(5) The Lungs.

The literature on the role played by the lungs is manifold. SPINA (40) claims for them dilatation. BRODIE & DIXON (39) believed that dilatation ovvurred if any effect at all was manifested. BIEDL (4) says that they constrict least of any organ, and probably are overcome by the blood pressure. Constriction, however, is the verdict of the majority of writers, including first VELICH (41) who first described this effect, also PLUMIER (42) PETITJEAN (43) LANGENDORFF (44) and finally most conclusively by WIGGERS (45) and by FUEHNER & STARLING (46) .

The last named writers have proved their point so conclusively, and have so well answered all objections and contra-findings, that we passed over this phase of the question as already settled, and without present warrant of further

investigation. The lungs, however, probably have no part in causing the initial rise of blood pressure because their constriction would merely reduce the sordiac output and so make for a fall in blood pressure.

(6) The Brain.

Authors who doubt or deny the existence of vasoconstrictors in the cerebral vessels claim that adrenalin has no effect upon the size of the brain. (See texts by Cushny, Howell, and Tigerstedt, quoted and referred to above).

SPINA (47) working in 1899 decided that the flow of the blood to the brain was increased, and this view is still held to by some modern workers (compare C ANNON, (16)) LANGLEY (32) described the brain as being "reddened" following adrenalin injections. Recent work by WIGGERS (48) however, who perfused the brain with a solution of proper osmotic pressure, indicates that the effect in the isolated brain is constriction. In no case did he obtain dilatation.

No experimental work on the brain was undertaken by us. Wiggers did his work upon an isolated brain, and it thus did not take into consideration the passive dilatation which might result from increased systemic blood pressure. (as is suggested by BIEDL (4))

Thus while from the literature it appears that the brain is probably not a factor of any considerable importance in causing the rise of blood pressure, the problem is still open

and is one that should be further investigated.

(7) The Thyroids.

No literature upon the role of the thyroids was found except a paper by HOSKINS (49) in which he showed that induced hyperthyreoidism stimulated a hyperplasia of adrenals. We extirpated the thyroids and observed no change whatever in the type curves from adrenalin injection.

(8) Uro-genital System.

Some scant literature upon the behavior of the organs was found, but we do not consider them of sufficient size in the normal animal to be of importance in the causation of so definite and extensive a phenomenon as the rise of blood pressure following the injection of adrenalin.

(9) The Intestines.

The literature concerning the behavior of the vessels of the intestines shows a striking difference from that concerning other organs, in that there is little or no difference of opinion. The unanimous conclusion is that the intestine vessels constrict. BIEDL (4) declares that they constrict more than any other organ. BRODIE & DIXON (39) perfused a portion of the intestines and showed a "marked constriction".

LANGLEY (32) calls attention to the marked pallor shown by the intestines following adrenalin administration. OLIVER & SCHAEFER (1) showed by plethysmographic records that the intestines, along with other organs innervated by the splanchnics (as originally proposed by LANGLEY) decrease in size.

Generally speaking, our work did not differ from this concensus of opinion. However, two facts should be noted in the literature just referred to.

(1) The doses used in all cases were far above the minimal.

(2) There is no statement of the time in the blood pressure curve in which the constriction of the intestinal vessels took place.

We regard these points, especially the latter one, as being of exceeding importance. It is probably on the strength of such work as the above that the conception of the intestinal vessel constriction being the cause of the rise of blood pressure has gained acceptance (vide supra).

Our own work may be summarized as follows:

Paying particular attention to the time in the cycle which the intestinal effect took place, we found by plethysmographic record in cats that a constriction was in all cases (with one exception) the primary effect of adrenalin injection, but in all cases THE CONSTRICTION TOOK PLACE DURING THE PERIOD OF HYPOTENSION.

In the DOG, using minimal doses and very small doses, the primary effect upon the intestines was usually dilatation.

This dilatation took place during the rise of blood pressure, and often extended over a period of the fall, as well. It was observed in 9 dogs in a total of more than 50 procedures.

In one dog a few records of a primary constriction were obtained, but this we attribute to the effect of larger doses. Later in the experiment the same dog gave a primary dilatation.

Extirpation of the ileum and jejunum in tote did not affect the blood pressure response to adrenalin in any apparent way.

Our CONCLUSIONS with regard to the role of the intestines during the rise of blood pressure, therefore, are that

(1) In the cat the intestinal vessels are primarily constricted by minimal doses of adrenalin intravenously, but not in time to cause the rise of blood pressure, since they occur during the period of hypotension.

(2) In the dog, the intestinal vessels are usually primarily dilated by minimal doses of adrenalin, intravenously, the dilatation occurring during the period of hypertension. This dilatation is doubless a passive one.

Thus in neither the dog nor the cat do the vessels of the intestines aid in causing the initial rise of blood pressure incident to minimal doses of adrenalin.

(10) The Legs.

The legs may be considered representative of the entire muscular system, and will be herein so considered.

That the legs constrict when perfused has been shown repeatedly, as mentioned by BIEDL (4) who adds that this constriction is less than other organs of the body. CANNON & NICE (50) ascribed the decrease in fatigue brought about by adrenalin to an increased blood flow to the muscles. NUEJEAN and also PARI are quoted in BIEDL as having found dilatation of the legs.

The actual results of our experiments were as follows: In the cat by perfusion, we got a constriction in 100% of cases. By plethysmographing, we obtained an enlargement in 21 cases out of 25. In a few cases a constriction was shown.

In the dog by perrusion we got opposite results in the two most definite experiments. In one case, using the float recording device of Wiggers, above described, we obtained dilatation followed by constriction in the first four trials, and after that only dilatation, due, possibly to the effects of the edema which ensued. In the other experiment, using the drop recorder, constriction occurred in 11 trials, and in the other two no effect was noted.

By plethysmographing we obtained results similar to those in the cat. In 6 experiments (about 40 cases) a primary enlargement took place, beginning during the rise and continuing over the period of the fall in many cases. Constriction occurred in a total of only three cases, and in these only with very large doses. Thus they may be discarded.

Our conclusions then, are that the effect of adrenalin

injected intravenously in minimal doses is to increase the size of the limb, although in the isolated limbs, perfusion usually shows constriction of the vessels. This paradox may be explained by one of two theories, either that the blood flow in the limb is actually increased, due to the high systemic pressure resulting from strong contraction in other organs, or that according to the theory of Oliver & Schaefer, the plethysmograph records an enlargement due to a marked constriction of the smaller vessels and an engorgement of the larger ones.

To summarize the discussion of the causation of the rise of blood pressure with minimal doses of adrenalin, injected intravenously, we find that the

Vaso-motor center and the brain may be of some slight aid.

That the heart, lungs, thyroids, bladder, uterus and intestines have no part in the causation of the rise.

That the skin, kidneys, and spleen are the most active agents in causing the rise.

.....

In support of the Oliver & Schaefer theory, it might be pointed out that these results were sporadic, the same type of response occurring frequently in the same experiment. Thus in Exp. 30, seven curves were obtained which showed a dilatation during the rise, followed by a secondary dilatation during the fall. In Exp. 31, thirteen times a constriction followed the primary dilatation. It is possible that this constant feature was due to the manner of applying the plethysmographs. It is obvious that the higher up on the leg the plethysmograph extends, the more large vessels would be included, and the more possibility of obtaining a dilatation rather than a constriction. Thus if the critical point were determinable in any one dog, a plethysmograph placed above that point on the leg might show one response, while if placed below it might show the exact opposite.

III. WHAT IS THE MECHANISM OF THE FALL OF BLOOD PRESSURE?

There are apparenty only two possibilities in determining the mechanism of the fall of blood pressure which follows the initial rise. It must be due either to cardiac or vaso-motor phenomena. In other words it seems most likely attributable either to a decreased cardiac output or to a vaso-motor dilation.

The theory of a decreased cardiac output does not occur in the literature to our knowledge, and it was first suggested by the work of FUCHNER and STARLING (46). Although present indications do not favor the theory, a consideration of it will not be out of place at this point.

As was pointed out in detail in the preceding section, although controversy upon the effect of adrenalin upon the heart rate has been great, the most recent work has indicated that the effect is retardation. BIEDL (4) states this as the current conception and it has been confirmed by workers in our own laboratory as well as by outsiders, Our own results are in agreement with this. MEEK & EYSTER (29) have shown that the vagal effect masks the direct stimulation of the heart muscle. However, if vagal tone be lowered by anethesia, exercise (See GASSER & MEEK. (28)) or otherwise, the direct effect overpowers the vagal effect and the heart is accellerated.

It will be recalled that we quoted abundant literature showing that the lungs are constricted by small doses of

adrenalin. It might be supposed, then, that the supply of blood to the heart would thus be decreased, the outflow of the heart therefore likewise decreased, and the fall of blood pressure be easily explicable by the resulting decrease in flow to the left heart.

This theory gains in plausibility when the slowing of the heart is taken into consideration. This, as we pointed out in the previous section, takes place during the rise of blood pressure and is continued for some time, including the period of hypotension.

To determine therefore, whether or not the output of the heart was actually decreased, we plethysmographed the hearts of both cats and dogs.

The results were quite conclusive. In most cases, due to the low vagal tone from the effects of the anesthetic and trauma, the heart rate was unaffected by the minimal doses. In these cases the output was markedly increased in every instance. Obviously in these cases, as well as in those cases where the rate was accellerated (which occurred but once) increased output would result unless a great diminution in the output per beat had resulted. But in all cases the output per beat was increased.

In some cases the characteristic slowing of the heart occurred. In these cases the actual output was carefully figured and in all cases measured, which included the most typical examples, the output was either unaltered or slightly increased.

To cite a typical example, in one case the increased output per beat averaged 22%, while the decrease in rate was 20%. Not only averages, however, but estimates of total volume per time unit were made, and in all cases confirmed these statements.

From these facts the conclusion is drawn that the phase of hypotension must be due to other than cardiac phenomena.

Turning to the theory of a peripheral vaso-dilatation as the cause of the fall of blood pressure in intravenous injections of adrenalin, we find this theory accepted by CANNON & LYMAN (20) who remark that "the vaso-dilatation is probably not confined to any one field of the body but affects alike the outlying limbs and the splanchnic areas".

Little additional general literature was found. The preceding section contained references to authors who drew conclusions regarding the action of specific organs, and the reader is referred to those references and citations.

It will be recalled that a great diversity of opinion prevails as to the action and role of the various organs of the body in adrenalin reactions. To summarize briefly our own conclusions with regard to certain organs, we may say that the SKIN, and SPLEEN are regarded as active only preceding and during the initial rise of blood pressure. The LUNGS, BRAIN, THYROIDS, and BLADDER are regarded as having little or no influence on the reaction.

The LIVER, KIDNEYS, EXTREMITIES and INTESTINES were deferred for a second discussion in this section relative to

their action during the phase of hypotension.

(1) The KIDNEYS.

Only the dog was used in determining the action of the kidney. Extirpation of both kidneys showed no apparent change, since the fall was obtained as often after the procedure as before. Perfusion showed constriction in every case, as stated above. Plethysmograph records showed, as stated above, in most cases a constriction during the rise of blood pressure.

During the fall in most cases, no effect was apparent. In one experiment, however, where a very sensitive piston recorder was used and a very good record obtained there was a distinct dilatation in five successive procedures, each time preceding in point of time the fall of blood pressure.

From this we conclude that the kidney sometimes plays a part in the causation of the fall of blood pressure by a dilatation preceding the systemic effect.

(2) The INTESTINES.

As shown in the preceding section, the usual primary effect of adrenalin upon a plethysmographed coil of the intestine was a marked increase in size, a dilatation, often lasting over the period of hypertension into the period of hypotension. This distension is largely a passive filling by virtue

of the high systolic pressure.

It should also be remembered that the cat gives a very slight rise followed by a marked fall with medium sized doses, and in the case of the dog the opposite relation exists. This may explain the absence of a dilatation from the plethysmographic records of the cat's intestines.

Our CONCLUSIONS, therefore, in regard to the role played by the intestines in the fall following intravenous injections of adrenalin are that the intestinal vessels play a passive role, or at best a very minor active one. They dilate passively during the rise (in dogs) and return to normal or constrict (in both dogs and cats). Thus they vary in size directly with the systemic blood pressure.

(3) The LIVER.

The plethysmographic records of the liver showed that in all cases its volume decreased during the fall of blood pressure. The constriction began during the decline of the blood pressure from its maximal point, and continues parallel with it fomr then until the two curves both return again to the normal.

This would indicate a passive response, similar to the response of the intestines during the fall. The point of difference is in the rise. It should be recalled that the main blood-volume of the liver is venous, and for this reason the rise in arterial pressure will probably have a much less marked effect upon its volume.

We CONCLUDE, from this preliminary experiment, that the liver probably is passively dilated during the fall in systemic blood pressure.

(4) The EXTREMITIES.

Here again we consider the legs as representative of the entire muscular system.

Perfusion occasionally showed dilatation, but usually constriction, as noted in the preceding section. But since we are unable to tell in what phase of the blood pressure curve these effects occurred, they are meaningless in seeking a cause for the fall.

Plethysmographic records showed that during the fall of blood pressure the usual change in the leg was a passive diminution in size. This applies only to dogs. In cats we obtained enlargement in three experiments, a total of 21 cases, and constriction in only one experiment, and then only three times.

In the dog we obtained a decrease in the size in a great majority of cases. Thus in a series of seven experiments with the leg plethysmograph, we obtained enlargement during the rise in six and constriction during the fall in five.

In the case of the cat, the evidence is upon the side of an active dilatation as a factor in the cause of the fall of blood pressure.

In the case of the dogs, however, the evidence is exactly contrary, unless one apply an extension of the theory

proposed by Oliver & Schaefer. According to this theory, the plethysmographic paradox would make the diminution in size correspond to a dilatation of the smaller vessels.

While we are not ready to accept this theory, for reasons advanced previously, certain facts tend to confirm it in this series of experiments.

(1) The plethysmographic paradox would be expected to work both ways upon the same animal, i.e. A reversal in the physiological reaction should show a reversal in the plethysmographic record, Hence we find support for the theory in the following data:

TABLE 9.

Showing	enlargement	during	the	rise:	Exp. ##	3, 17, 29, 30, 31.
"	constriction	"	"	fall:	"	4, 17, 29, 30, 31.
"	"	"	"	rise:	"	5, 30.
"	enlargement	"	"	fall:	"	30.

Still another argument might be made of the fact that since the area of the capillary bed is greater than the area of the large vessels of the limb, a full dilatation of them would far outmeasure the volume contained in a full dilatation of the large vessels. Hence it might be deduced that the constriction during the fall would probably be less than the dilatation during the rise. This proved by our records to be actually the case (See Experiment 17, Proc. 12) In some cases it does not hold true, due doubtless to the slight rise and the large fall occurring in some instances.

In fact those cases where a secondary dilatation occurred during the phase of hypotension, might be explained by supposing that a larger dilatation of the smaller vessels took place in those cases, overpowering the shrinkage effect of the larger vessels. See Experiment #30.

Our CONCLUSIONS, therefore, in regard to the role of the vessels of the extremeties in the fall of blood pressure following injections of adrenalin, are:

1. In the cat, where the fall is most marked,the vessels of the muscular system may dilate actively and thus aid in causing the fall, although perfusion did not confirm this.

2. In the dog, an enlargement of the leg during a rise of the blood pressure is usually followed by a diminution in the size of the leg during the fall of blood pressure. Although we are not ready to accept the theory proposed by OLIVER & SCHAEFER as to the paradoxical registering made by the plethysmograph, certain facts in this series of experiments confirm the possibility, that there is actually an active dilitation of the smaller vessels. The arguments favoring this view are thus sumarized:

(1) The same experimental animals which gave the paradoxical dilatation during the constriction (i.e. during the period of hypertension) gave a constriction during the period of hypotension.

(2) Likewise the same animals which showed a constriction of the leg volume during the hypertension, showed a diminished volume during the hypotension.

(3) The constriction during the hypotension is less in extent than the dilatation during the hypertension; in fact it is so much less in some cases that it becomes a dilatation. (Since the area of the dilated capillary bed is greater than the area of the dilated arterial bed.)

(5) The ADRENAL GLANDS.

We attempted several experiments in which we tested for the depressor element in the curves before and after extirpation of the adrenal glands. In all cases but the last, however, our experiments were rendered worthless by minor mishaps. In one case we found by post-mortem that a portion of one gland had not been tied off. In another we worked with a dog which gave very few falls and made comparison worthless.

In an experiment performed May 28, however, we obtained some striking data. It may best be presented in table form:

TABLE 10. Experiment 32.

	BEFORE ADRENAL EXTIRPATION	FOLLOWING ADRENAL EXTIRPARION
Percentage of falls occurring	66%	35%
Maximum depth of falls occurring	20.5 mm.	2.5 mm.
Average depth of falls occurring	13 mm.	2.0 mm.
Minimal depth of falls occurring	4 mm.	1 mm.

In addition to these suggestive facts, two subcutaneous doses of 2 cc. of a 1/25,000 solution failed to give

a fall after the operation. As we shall show later, in other animals there was always produced the effect of a marked primary fall. Unfortunately we did not test this dog in this regard previous to tying off the adrenals.

Another fact which points in this same direction is that in a summary of our entire experimental work it appears that most of the large falls, and most of the pure falls occur early in the experiments. It is suggested that the fall, if due to the effects of stimulation of the adrenals, by the injection of adrenalin would be decreased late in the experiment due to the diminished quantity of adrenalin available in the animals glands.

This might also explain in large degree the difference in response in some animals in giving falls. An animal who thru a recent severe excitement had lost considerable adrenalin would thus give much fewer falls than an animal which for some time had been living a quiet, non-stressed life.

Our CONCLUSIONS, therefore, are that from the indications of a preliminary experiment, the fall of blood pressure is in some way dependent upon the adrenal glands of the animal since

(1) Falls occurring after extirpation are less numerous, and far less marked. In view of the existence of accessory chromaphil tissue, it is not to be expected that the falls will disappear entirely upon extirpation of the adrenals only.

(2) In a long series of experiments, it was noted that more falls occurred toward the beginning than toward the

end of the experiments, possibly due to a diminishing in the supply of the adrenal secretion as the experiments progressed.

Regarding the causation of the fall of blood pressure following injections of adrenalin, a summary of our conclusion is, briefly:

(1) That the heart is probably not responsible.

(2) That the passive dilatation of the vessels of the liver and intestines may be of slight aid in causing hypotension.

(3) That the kidneys may sometimes actively assist in causing the fall.

(4) That the vessels of the muscles may actively assist.

(5) That in some way the fall of blood pressure is dependent upon the adrenal glands of the subject.

IV. CERTAIN SECONDARY OBSERVATIONS.

1. The theory of the operation of epinephrin to cause first constriction and then dilatation as offered by CANNON & LYMAN, we do not feel able to accept. These authors suggest that the difference in action was due to a dual response of the muscles to the same stimuli, depending upon their state of tonus.

To disprove this, we resorted to the simple procedure of testing the response of a dog before and after lowering

vaso-motor tone. In order to lower tone without trauma, we made use of the well known phenomenon that a dog held in an upright position suffers from great hypotension due to the dilatation of the splanchnic vessels. In this way we lowered the blood pressure of a dog from 90 mm to 36 mm. In every trial the same effect was evinced by injection of adrenalin after this procedure as before.

(2) The explanations offered by McQuigan & Mostrom, (23) for the depressor effect of adrenalin were considered in the introductory statement. Three of them, however, were deferred for answer to this point.

#3, that the depressor effect is due to fatigue products, and #5 that it is due to the nervous shock resulting from repeated doses of adrenalin are both disproved by the repeated instances in which we were able to obtain a fall in the first injection of an experiment. In one series of experiments we obtained falls in the case of the first injection in 10 cases, in the case of the 2nd injection in 10 cases, and in the case of the third injection in 11 cases.

The fourth explanatory factor offered by McQUIGAN and MOSTROM, that the depressor effect depends on individual peculiarities of the animals, is not to be gainsaid. Certain animals, we will grant, exhibit a striking tendency to show pure rises, or again pure falls, but this does not indicate that either the pure rise or the pure fall effect is abnormal. Certain animals to illustrate, show profuse salivation upon anesthetizing, but because others do not show salivation may not be considered as indicative that salivation is an

individual peculiarity.

(3) The physiological action of adrenalin HCl, P.D. and Abel's epinephrine differ markedly in certain respects. These should be investigated in seeking for the actual explanation of the action of adrenalin. The main point of difference observed by us (using cats) was that P.D. salt never gives a primary fall, and gives comparatively few rises. Epinephrine, on the other hand, gives many pure rises and many pure falls in the same animals in which P.D. Adren HCl fails to give either.

(4) There is commonly observed in blood pressure changes following the injection of a dose of adrenalin a peculiar oscillation of the manometer prior to the event of a marked rise or fall. This oscillatory movement is S shaped, and consists of a slight rise, a slight fall, and a return to the normal line.

For some time we were unable to explain this phenomenom, and found no mention of it in the literature, although it is reproduced in some of the curves shown in current articles. In giving very dilute doses it was occasionally of considerable annoyance, due to the fact that it interfered with the determination of slight rises and slight falls.

After some investigation we determined this preliminary S shaped curve to be due to nothing more than the physical effect of the rapid injection of a fluid solution of considerable bulk, since:

1. It occurs in larger sized doses, 1-2cc.

2. It never occurs in small sized doses.

3. It takes place immediately after the time of injection.

4. It thus occurs before any physiological effect would be possible.

5. It occurs with water controls.

(5) Injections of adrenalin into the connective tissue spaces of dogs produces constantly a primary fall of blood pressure, followed by a secondary rise. A dose which intravenously caused a primary rise, when injected subcutaneously repeatedly caused a primary fall. Injected intramuscularly brought the same result; injected intraperitoneally again the same result.

This phenomenom was noted by MELTZERS (19) by GOTTLIEB (51) by BORUTTAU (52) and by LEWANDOWSKY (53).

It might be explained in one or two ways. Either there is a dilution or an attenuation of the dose to a degree which stimulates the dilators before the constrictors, or else a change in the chemical nature occurs which alters the physiological effect.

It has occurred to us that this effect upon subcutaneous injection, and likewise the commonly observed action of adrenalin, might be harmonized by the following theory.

Since in both cases the adrenalin passes over considerable lengths of blood vessel intima, and since as shown by TATUM (54) in this University, the intima finally renders the adrenalin inert by decomposition.

The depresser effect might be caused by a primary decomposition product i.e. before the end product, which is

inert, is formed. Thus in cases where the adrenalin must first be absorbed and carried to the heart and then distributed, i.e. in subcutaneous doses, the amount of intima passed over is much greater and decomposition takes place more completely, leaving none of the pressor substance and only the depressor substance which, as we propose, may be only an intermediary product of decomposition.

The reason the depressor effect does not occur in maximal doses in the dog, then, might be explained on the basis that the persistance of the great pressor effect masks its action.

In view of the suggestion made in the preceding section of this paper with regard to the possible function of the adrenal gland in producing the depressor effect, it might be necessary to interpose the condition that a product of the adrenal gland was necessary, either by combination or catalysis, to produce the depressor product of decomposition.

SUMMARY.

The action of adrenalin injected intravenously varies in different animals.

(a) In the rabbit the effect of a minimal dose is a rise followed by a fall. A somewhat larger dose gives a pure rise. A still larger dose usually gives a pure fall. A still larger dose frequently causes death.

(b) In the cat the effect of the minimal dose is probably to cause a pure rise. A slightly larger dose causes primary fall. A larger dose causes usually a rise followed by a marked fall.

(c) In the dog, the minimal effect is definitely a pure rise. Slightly larger doses give a rise and fall, and still larger doses give a rise not followed by a fall.

The rise of blood pressure probably results from the constriction of the skin, the kidney, and the spleen, together with certain other organs not yet definitely settled.

The fall of the blood pressure possibly results from active dilatations in certain organs, e.g. the kidneys. A passive or feebly active dilatation occurs in the intestines and liver. But these are very impotent of causing a marked fall. In the case of the cat, an active dilatation takes place in the vessels of the muscles.

The heart rate is normally slowed by adrenalin in the intact animal, although the cardiac output is increased during the phase of hypotension.

The adrenal glands are apparently concerned in the

production of the depressor phase of blood pressure during adrenalin injection.

The depressor effects are certainly not due to decomposition products, nervous shock, or fatigue products, as suggested by some authors. (The last named rather decreases than increases the tendency to give a depressor effect)

We cannot accept the theory of Cannon as to the dual response of the vasoconstrictors, due to the fact that it is possible to secure a fall with low blood pressure.

The preliminary S curve observed in some Blood pressure curves is due to a physical effect, not a physiological one.

Injections of adrenalin into a dog's connective tissue spaces is commonly followed by a fall of blood pressure, if the adrenals are intact.

A theory as to the action of adrenalin in producing in some cases rises, in some cases falls, and in some both rises and falls is proposed.

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